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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/786,435	03/20/2001	Kerstin Krieglstein	MBP-005XX	1324

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EXAMINER	
FORD, VANESSA L	

ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/786,435	KRIEGLSTEIN, KERSTIN	
	Examiner	Art Unit	
	VANESSA L. FORD	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 14-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 14 -18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

FINAL ACTION

1. Applicant's amendment and response filed December 5, 2007 is acknowledged. Claims 2-13 have been cancelled. Claims 16-18 have been amended. Claims 1 and 14-18 are under examination.

Rejection Withdrawn

2. In view of Applicant's amendment filed December 5, 2007, the rejection of claims 16-18 under 35 U.S.C. 112, second paragraph is withdrawn.

Rejections Maintained

3. The rejection of claims 1 and 14-15 under 35 U.S.C. 102(b) as anticipated by Logan is maintained for the reasons set forth on page 3-4, paragraph 3 of the previous Office Action.

The rejection is reiterated below.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Logan et al teach that the present invention generally relates to CNS injuries and more particularly the presence of TGF-β1 in injured CNS tissues (page 3). Logan et al teach that the there is a potential use for TGF-β1 antagonists (inhibitors) as adjunct to those therapies designed to promote regeneration and reconnection of damaged neural pathways (page 8). Logan et al teach that antagonists include neutralizing TGF-β1 antibodies, decorin and its functional equivalents such as biglycan (page 3). Therefore the prior art reference teaches preventing apoptosis. Logan et al teach that animals

underwent a craniotomy (example II). Logan et al teach that three days after the induced injury, oedma in the wound was still extensive (Example VI). Logan et al teach that neutralizing antibodies were infused into the wound (Example III, page 19). Logan et al teach that after infusion of the wound with neutralizing antibodies(anti-TGF-β1 antiserum), there was complete absence of immunoreactive fibronectin within the wound and a reduced number of macrophage/microglial cells when compared to control (page 20). Therefore, Logan et al teach a method of treating damaged neurons (pages 20-21). Logan et al anticipate the claimed invention.

Applicant's Arguments

Applicant urges that Logan et al describe the prevention of scar formation on blood-derived cells. Applicant urges that this is a different population of cells from the cells used in the claimed method. Applicant urges that Logan et al describes treating astrocytes and fibroblasts and the claimed invention is concerned with neurons.

Examiner's Response to Applicant's Arguments

Applicant's arguments filed December 5, 2007 have been considered but are not persuasive. Logan et al teach methods of preventing, suppressing or treating central nervous system pathologies by administering neutralizing ant-TGF-β antibodies or TGF-β antagonists (see the Abstract). Logan et al teach that TGF-β1 is produced by cells with damaged tissue (pages 6-7). Logan et al teach that the TGF-β antagonists of the invention can be used as adjunct to therapies designed to promote regeneration and reconnection of damaged neural pathways (page 8). Thus, Logan et al teach method of treating using TGF-β antibodies or TGF-β antagonists that interact with neutral pathways. Thus, Logan et al teach treating or preventing damaged neurons.

In view of all of the above this rejection is maintained.

4. The rejection of claims 1, 14 -15 and 18 under 35 U.S.C. 102(b) as anticipated by Melton et al is maintained for the reasons set forth on page 3-5, paragraph 4 of the previous Office Action.

Melton et al teach the a method of preventing or antagonizing a signal pathway in a cell for a growth factor of transforming growth factor β (TGF-β)(page 4). Melton et al teach that the antagonizing agent can inhibit the biological activity of the TGF-β type growth factor, for example, preventing the growth factor from binding its receptors on the surface of the treated cells (page 4). Melton et al teach that the antagonizing agent is selected from the group consisting of follistain module, and a truncated receptor for growth factor TGF-β family (page 4). Melton et al teach that the antagonizing agent of the invention can bind to growth factor and sequesters the growth factor such that it cannot bind its receptors (page 4). Melton et al teach that the invention can be used to treat neurodegenerative disorders including anoxia-ischemia (page 5). Melton et alt each that the method comprising contacting a cell wither in vivo or in vitro with an agent cable of antagonizing the biological action of a protein from the family of transforming growth factor -β (page 5). Melton et al teach that the antagonizing agents can be administered by many administration routes such as intravenous and oral administration (page 19). Melton et al teach that the present method is amenable to therapeutic application of neurodegenerative disorders that are progressive and persistent loss of neuronal cells such as Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerois and Huntington's disease (page 6). Melton et al anticipate the claimed invention.

Applicant' s Arguments

Applicant urges that Melton et al does not anticipate the claimed invention. Applicant urges that Melton et al disclose specifically administering activin or any other member of the TGF-β family that interacts with the truncated activin receptor. Applicant urges that Melton et al disclose inhibition of the neural induction by activin but not TGF-β1, TGF-β2 or TGF-β3.

Examiner's Response to Applicant's Arguments

Applicant's arguments filed December 5, 2007 have been fully considered but they are not persuasive.

Melton et al teach that treatment of patients suffering from degenerative conditions can include the application of neutralizing polypeptides or agents which mimic their effects in order to manipulate apoptosis of neurons which give rise to the loss of neurons. Melton et al discloses a method for inducing neuronal differentiation and preventing the death or degeneration of neuronal cells *in vivo* by antagonizing a signaling pathway for a growth factor of the TGF-β family and pharmaceutical preparations comprising a neutralizing agent capable of antagonizing said pathway. Melton et al further teach that therapeutic applications of agents that are encompassed by the invention (e.g. activin antagonist) can be used alone or in conjunction with other neurotrophic factors to prevent or reverse motor neuron degeneration in patients suffering from disorders such as ALS. Thus, it is the Examiner's position that the prior art reference anticipates the claimed invention.

5. The rejection of claims 1 and 14-17 under 35 U.S.C. 103(a) as unpatentable over Logan in view of Alexander et al is maintained for the reasons set forth on pages 5-7, paragraph 4 of the previous Office Action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Logan et al that the present invention generally relates to CNS injuries and more particularly the presence of TGF-β1 in injured CNS tissues (page 3). Logan et al teach that the there is a potential use for TGF-β1 antagonists (inhibitors) as adjunct to those therapies designed to promote regeneration and reconnection of damaged neural pathways (page 8). Logan et al teach that animals underwent a craniotomy (example II). Logan et al teach that three days after the induced injury, oedma in the wound was still extensive (Example VI). Logan et al teach that neutralizing antibodies were infused into the wound (Example III, page 19). Logan et al teach that after infusion of the wound with neutralizing antibodies(anti-TGF-β1 antiserum), there was complete absence of immunoreactive fibronectin within the wound and a reduced number of macrophage/microglial cells when compared to control (page 20). Therefore, Logan et al teach a method of treating damaged neurons (pages 20-21).

Logan et al do not teach the claim limitation the method of 1, wherein said method further comprises treating said patient with a compound for disintegrating blood clots.

Alexander et al teach that urokinase and anticoagulants are recommended for treatment when patients are at risk for cerebral hemorrhage (see the Abstract). Alexandria et al teach that tissue plasminogen activator is effective in lysing blood clots in animals (see the Abstract).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to add the urokinse or tissue plasminogen activator of Alexandria et al to the pharmaceutical compositions used in the method of Logan et al because Alexander et al teach that urokinase and anticoagulants are recommended for treatment when patients are at risk for cerebral hemorrhage such as the patients with CNS pathologies as taught by Logan et al and Alexander et al has shown that tissue plasminogen activator is effective in lysing blood clots in animals. It would be expected absent evidence to the contrary, that the addition of urokinase or tissue plasminogen activator would disintegrate blood clots because it is well known in the art that the prevention of blood clots would be necessary for treatment of central nervous systems disorders.

Applicant's Arguments

Applicant urges that a combination of Logan et al and Alexander et al still will not teach or make obvious the deficiencies listed in the primary reference. Applicant urges that Logan et al nor Alexander et al teach the claimed invention.

Examiner's Response to Applicant's Arguments

Applicant's arguments filed December 5, 2007 have been fully considered but they are not persuasive.

In response to Applicant's arguments regarding the combination of references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Logan et al teach pharmaceutical compositions comprising agents including anti -TGF-β antibodies and TGF-β antagonists) to inhibit the activity of TGF-β in the central nervous system. Logan et al teach that these inhibitors can be formulated with pharmaceutically acceptable carriers. Logan et al do not teach compounds for the disintegrating blood clots. However, Alexander et al teach that urokinase and anticoagulants are recommended for treatment

when patients are at risk for cerebral hemorrhage and disintegrating blood clots. One of skilled in the art would be motivated to add the urokinase and plasminogen activator to a composition comprising TGF-β inhibitors because Alexander et al teach that urokinase and anticoagulants are recommended for treatment when patients are at risk for cerebral hemorrhage. Thus, a composition comprising -TGF-β antibodies and TGF-β antagonists, urokinase and anticoagulants would be effective in a method for treating predamaged neurons. There is nothing on the record to suggest that the combination of prior art references do not teach the claimed invention.

In view of all of the above, this rejection is maintained.

6. The rejection of claims 1 and 14-18 under 35 U.S.C. 103(a) as unpatentable over Melton et al in view of Alexander et al is maintained for the reasons set forth on pages 7-10, paragraph 6 of the previous Office Action. The rejection is reiterated below.

Claim 1, 14-16 and 17-18 are rejected under 35 U.S.C. 103(a) as unpatentable over Melton et al *(WO 95/10611, published April 20, 1995).* in view of Alexander et al *(Neurosurgery, 1990, 26/4, p. 559-564).*

Melton et al teach a method of preventing or antagonizing a signal pathway in a cell for a growth factor of transforming growth factor β (TGF-β)(page 4). Melton et al teach that the antagonizing agent can inhibit the biological activity of the TGF-β type growth factor, for example preventing the growth factor from binding its receptors on the surface of the treated cells (page 4). Melton et al teach that the antagonizing agent is selected from the group consisting of follistain module, and a truncated receptor for growth factor TGF-β family (page 4). Melton et al teach that the antagonizing agent of the invention can bind to growth factor and sequesters the growth factor such that it cannot

bind its receptors (page 4). Melton et al teach that the invention can be used to treat neurodegenerative disorders including anoxia-ischemia (page 5). Melton et alt each that the method comprising contacting a cell wither in vivo or in vitro with an agent cable of antagonizing the biological action of a protein from the family of transforming growth factor -β (page 5). Melton et al teach that the antagonizing agents can be administered by many administration routes such as intravenous and oral administration (page 19). Melton et al teach that the present method is amenable to therapeutic application of neurodegenerative disorders that are progressive and persistent loss of neuronal cells such as Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerois and Huntington's disease (page 6).

Melton et al do not teach the claim limitation the method of 1, wherein said method further comprises treating said patient with a compound for disintegrating blood clots.

Alexander et al teach that urokinase and anticoagulants are recommended for treatment when patients are at risk for cerebral hemorrhage (see the Abstract). Alexandria et al teach that tissue plasminogen activator is effective in lysing blood clots in animals (see the Abstract).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to add the urokinse or tissue plasminogen activator of Alexandria et al to the pharmaceutical compositions used in the method of Melton et al because Alexander et al teach that urokinase and anticoagulants are recommended for treatment when patients are at risk for cerebral hemorrhage such patient that would have the disorders as disclosed by Melton et al and Alexander et al has shown that tissue plasminogen activator is effective in lysing blood clots in animals. It would be expected absent evidence to the contrary, that the addition of urokinase or tissue plasminogen activator would disintegrate blood clots because it is well known in the art that the prevention of blood clots would be necessary for treatment of central nervous systems disorders.

Applicant's Arguments

Applicant urges that a combination of Melton et al and Alexander et al still will not teach or make obvious the deficiencies listed in the primary reference.

Applicant urges that Melton et al nor Alexander et al teach the claimed invention.

Examiner's Response to Applicant's Arguments

Applicant's arguments filed December 5, 2007 have been fully considered but they are not persuasive.

In response to Applicant's arguments regarding the combination of references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Melton et al teach a method of preventing or antagonizing a signal pathway in a cell for a growth factor of transforming growth factor β (TGF-β). Melton et al do not teach compounds for the disintegrating blood clots. However, Alexander et al teach that urokinase and anticoagulants are recommended for treatment when patients are at risk for cerebral hemorrhage and disintegrating blood clots. One of skilled in the art would be motivated to add the urokinase and plasminogen activator to a composition comprising TGF-β inhibitors because Alexander et al teach that urokinase and anticoagulants are recommended for treatment when patients are at risk for cerebral hemorrhage. Thus, a composition comprising -TGF-β antibodies and TGF-β antagonists, urokinase and anticoagulants would be effective in a method for treating

predamaged neurons. There is nothing on the record to suggest that the combination of prior art references do not teach the claimed invention.

In view of all of the above, this rejection is maintained.

Status of Claims

7. No claims allowed.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vanessa L. Ford whose telephone number is (571) 272-0857. The examiner can normally be reached on 9 am- 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on (571) 272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Vanessa L. Ford/
Examiner, Art Unit 1645
March 17, 2008

/N. M. Minnifield/
Primary Examiner,
Art Unit 1645